Wound healing outcomes: Using big data and a modified intent-to-treat method as a metric for reporting healing rates

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ABSTRACT

Chronic wounds are increasing in prevalence and are a costly problem for the US healthcare system and throughout the world. Typically outcomes studies in the field of wound care have been limited to small clinical trials, comparative effectiveness cohorts and attempts to extrapolate results from claims databases. As a result, outcomes in real world clinical settings may differ from these published studies. This study presents a modified intent-to-treat framework for measuring wound outcomes and measures the consistency of population based outcomes across two distinct settings. In this retrospective observational analysis, we describe the largest to date, cohort of patient wound outcomes derived from 626 hospital based clinics and one academic tertiary care clinic. We present the results of a modified intent-to-treat analysis of wound outcomes as well as demographic and descriptive data. After applying the exclusion criteria, the final analytic sample includes the outcomes from 667,291 wounds in the national sample and 1,788 wounds in the academic sample. We found a consistent modified intent to treat healing rate of 74.6% from the 626 clinics and 77.6% in the academic center. We recommend that a standard modified intent to treat healing rate be used to report wound outcomes to allow for consistency and comparability in measurement across providers, payers and healthcare systems.

In 2009, in the US alone, there were an estimated 6.5 million individuals suffering from chronic wounds resulting in a $25 billion cost to the healthcare system.[1] As the population ages and the number of patients with both obesity and diabetes increases, chronic wounds will become one of the most relevant medical conditions worldwide.[2] The escalating cost of wound care treatment has created a $15.3 billion dollar wound care product market in 2010.[1] Due to changes in healthcare legislation and a transition toward fee for value, there is a need to decrease the cost of wound treatments while preserving quality. This is especially pertinent for clinical fields in which patients suffer from multiple comorbidities, and require costly treatment.[3] Wound care is emerging as a subspecialty and yet there is currently no standard or approved method for reporting the most important fundamental clinic based outcome, wound healing. Results from clinical trials are most frequently reported by a wound specific etiology. Comparing results from randomized controlled trials and emerging databases, the methods for reporting healing rates are inconsistent and susceptible to bias. Published healing rates vary and it is often difficult to determine which cases were included or excluded from the final analysis. Compare this to Oncology where data exists not only on specific cancer types in clinical trials but also at the macro level there are indications of cancer outcomes changing over time in the aggregate.[4] Oncology also has moved toward coordinated efforts between providers to gain consensus and standardize outcomes metrics and transition toward patient centric and patient reported data points.[5] Oncology also employs a staging system that allow for risk stratification, prediction of outcomes and the appropriate selection of therapeutic treatments for a corresponding stage. This has allowed Oncology to move toward personalized medicine using biomarkers and genomics to identify and personalize cancer care for patients.[6,7]

The goal of this study is to articulate a standardized aggregate outcome reporting method for chronic wounds. To achieve this objective, we analyze healing rates form a large database of wound healing outcomes generated by a wound care management company (Healogics, Jacksonville, FL) operating 626 acute care hospital based wound care clinics and subsequently compare the results to healing outcomes at an academic clinical team working at a satellite, hospital-based wound clinic. We found consistency of results and as a result we propose an empirically

based process for reporting healing rates that will create a standardized method for comparing outcomes across various settings. Further analyzing the healing rates using different inclusion criteria allows for more detailed analysis allowing centers to review and improve their quality processes.[8] This approach will provide the language necessary to enable providers to describe standardized wound specific outcomes and move toward risk stratification, utilize predictive analytics and ultimately assess the relevance of biomarkers and genomics for personalized wound care.

METHODS

The lead author has previously used an intent to treat (ITT) methodology from both outpatient clinics and across various sites of care.[9,10] These studies demonstrated the ability to analyze healing trajectories, and percentage healing at various time points in various clinical settings. Using the prior work as a starting point, this retrospective observational analysis updates the previously reported outcomes using descriptive data from a large cohort of outpatient wound care center wounds.

National cohort of wound centers

Retrospective data including wound location, patient demographics, and final disposition were collected from 626 outpatient wound care centers nationwide between January 1, 2014 and November 1, 2015. The timeframe for data inclusion was determined by the availability of aggregate wound data at the time of analysis. The data used for the study were compiled into a deidentified research database table distinct from the enterprise data warehouse prior to the beginning of the analysis. All patient identifiers were removed from the research file. All wounds that met the qualifying inclusion criteria were included in the deidentified file, no other exclusions were applied.

All centers in the sample were managed by a wound care management company and staffed by a provider panel that consisted of a combination of contract physicians in private practice and a subset of employed providers who practiced wound care full-time. All clinicians were required to attend a 1-week specialty wound care training course and were provided evidence based algorithmic clinical practice guidelines. The clinicians subsequently receive ongoing education, monthly conference calls and have access to regional and local medical directors for case management support. All programs are hospital based and have program directors, managers, and nurses with most programs having access to hyperbaric oxygen and needed specialty consultants. The clinicians in these centers have well designed and standardized quality of care processes supporting clinical protocols to ensure the consistent delivery of care. All patients who had a wound, had more than seven days between first and last assessment, and were not still in active treatment at the time of study closure were included in the modified intent-to-treat sample. The data were obtained from a proprietary clinical database and collected using a specialized wound data capture system that tracks wound related treatments and patient outcomes. Nurses and physicians document visits at point of care. A subset of centers document using paper-based forms which were then entered into a central system at the end of each work day. Other centers document visits on a fully electronic medical record basis. Deidentified data were extracted using SQL software and analyzed using Stata/MP 14.1. (StataCorp, College Station, TX)

Academic wound center

Data from 2006 to 2009 were prospectively collected and retrospectively analyzed. The data were generated from a 200 bed, community hospital based wound care program staffed by 3 full time wound program faculty of the University of Illinois Hospital. This center was not affiliated with Healogics. The primary author was the medical director; another physician, who had just completed a one year clinical wound fellowship, and an advanced practice nurse with 12 years of wound care experience made up the clinical team. The data were entered into an electronic medical record and then double entered each day into a secure excel based research spread sheet by a full-time Ph.D. director of research The center had hyperbaric oxygen therapy capabilities and a fully integrated physical therapy program. Standardized protocols and procedures were constant during the data collection period. Data collection included demographic information as well as wound etiology, wound type and location, wound measurements, treatment duration, and final disposition. Wound photographs were used at each visit and measurements were conducted both manually and through the use of grid film technology and/or digital planimetry. The data were retrospectively analyzed using SPSS analytical software (IBM Corporation, Armonk, NY). All subjects included in this study received comprehensive wound care treatment according to established protocols created and published by the authors.[11] Advanced wound care products and wound modalities, as well as specialized orthotics and prosthetics consultations were available when indicated.[12] All patients who had a wound, had more than one visit, and were not still in active treatment at the time the study closure were included in the modified intent-to-treat sample. The protocols used by Healogics are in complete alignment with those utilized by the clinicians at the University wound center. The data were captured from the clinic opening until the program was moved back to the University and the satellite location was closed.

Variables

The primary variable of interest is the modified Intent-to-Treat (mITT) wound outcome. This variable is defined as the percentage of all nonactive, nonconsultation wounds, with greater than seven days between first and last assessment that were healed. We report outcomes as the percentage of wounds healed as well as the percentage of patients with all wounds healed.

Other variables assessed include, patient demographics such as age and sex, as well as wound location and final patient disposition.

RESULTS

National cohort of wound centers

From the 2014–2015 sample of 412,687 patients with 1,006,690 wounds seen in (Healogics Inc., Jacksonville, FL) the wound care centers from January, 2014 to November, 2015 and after including only patients who had a wound, had more than one visit, and were not still in active treatment at the time the study closure, the modified intent-to-treat cohort consisted of 284,719 patients with 667,291 total wounds. A total of 117,517 patients had all wounds healed for a patient level healing rate of 60.2%. At the wound level, we found 498,117 healed wounds from the total of 667,291 wounds for a 74.6% healing rate. The mean age of the patients was 65 years with 53% men and 47% women (Table 1). The most common wound location was the lower extremity and foot comprising a total of 76% of all wounds (Table 2). Table 3 shows the healing rates using various other inclusion criteria.

Academic clinic cohort

From 2006 to 2009, a total of 1,111 patients with 2,578 wounds were included in the database. Of those 1,111 patients, 268 patients (652 wounds) were consult only, 34 patients with 63 wounds reported actually had no open wound, and 46 patients (75 wounds) were still in active treatment when the data collection period ended. Thus, a total of 763 patients with 1,788 wounds were included in the modified intent-to-treat data analysis and were then subjected to formal analysis.

There were 471 patients in which all of their wounds healed (471/763 61.7%). Analyzing the data at the wound level, 1,388 out of 1,788 wounds (77.6%), healed (Table 4). The population consisted of 55% women and 45% men and mean age of 61.7 years (Table 1). Wounds were distributed throughout the body but the majority was on the lower extremity and feet comprising 83% of all wounds (Table 2). There were 21 patients who died before they were completely healed. The patients in this category had a total of 37 wounds, 35 of which were not healed at the time of death and 2 wounds that were healed at the time of death. There were patients who went to other providers or sites of care and did not return to the clinic. Some of these patients had more than one wound and, therefore, might have transferred care with some of the wounds healed, none of them healed or a combination. A number of patients were simply lost to follow-up and this category accounted for an additional 82 wounds not having a final disposition. A total of 45 patients were placed on palliative care with 202 total wounds.

Similar outcomes were achievable between senior and junior physician faculty, as well as an experienced APN (Table 5). "Provider" analysis can help demonstrate differences between physicians and some mid-level providers.

DISCUSSION

This study demonstrates, for the first time, that using a consistent care plan combined with a standardized methodology to calculate healing rates that well managed wound clinics can expect an average aggregate healing rate of 75–78%. These results are comparable to those achieved at an academic program. This report describes the largest published data set of wound healing in the literature and recommends the use of a modified ITT methodology.

The negative impact of noncompliance and missing data has led many to believe that using an ITT model is the best approach to analyze outcomes. The ITT analysis includes all randomized patients in the groups initially assigned regardless of their adherence with the entry criteria, treatment actually received, withdrawal or deviation from the protocol.[13] Authors refer to ITT as "once randomized, always analyzed."[14] The Food and Drug Administration (FDA) utilizes this trial design for industry based clinical trials and it is also widely used in government sponsored research.[15–17]

Table 1. Demographics

	2014–2015	2006–2009
Female	47.46%	55.00%
Male	52.54%	45.00%
Age	64.99 years	61.7 years

Table 2. Wound locations

	2014–2015 #/%	2006–2009 #/%
Amputation site	10,782	0
	1.62	0
Abdomen	26,262	78
	3.94	4.36
Chest/breast	4,411	19
	0.66	1.06
Lower leg	265,501	960
	39.79	53.69
Head/neck	7,105	2
	1.06	0.11
Coccyx	11,232	33
	1.68	1.85
Upper limb	37,136	15
	5.57	0.84
Toe	81,651	131
	12.24	7.33
Pelvic	53,343	99
	7.99	5.54
Back	6,965	34
	1.04	1.90
Foot	161,302	394
	24.17	22.04
Other	1,601	23
	0.24	1.29
Total	667,291	1788
	100	100

Table 3. Modified intent-to-treat

	2014–2015	2006–2009
Total # healed wounds	498,113	1,388
Total # wounds	1,006,690	2,578
% healed at population level	49.5	53.8
Exclude # active at study conclusion	99,301	75
% of total	9.9	2.9
# remaining wounds	907,389	2,503
% healed at level	54.9	55.5
Exclude # without wound documented	4,080	63
% of total	0.4	2.4
# remaining wounds	903,309	2,440
% healed at level	55.1	56.9
Exclude # consult and with days first to last assessment <= 7 days	236,018	652
% of total	23.4	25.3
Final # remaining wounds	667,291	1,788
% healed at level mITT	74.6	77.6
Total # healed wounds	498,113	1,388
Total # wounds	1,006,690	2,578
% healed at level mITT	74.6	77.6
Exclude # wounds patients that died	15,867	35
% of total	1.6	1.4
# remaining wounds	651,424	1,753
% healed at level	76.5	79.2
Exclude # wounds patients that moved	5,520	4
% of total	0.6	0.2
# remaining wounds	645,904	1,749
% healed at level	77.1	79.4
Exclude # wounds patients that transferred providers	24,436	34
% of total	2.4	1.3
# remaining wounds	621,468	1,715
% healed at level	80.2	80.9
Exclude # wounds patients that transferred facility	66,776	48
% of total	6.6	1.9
# remaining wounds	554,692	1,667
% healed at level	89.8	83.3
Exclude # wounds patients lost to follow-up	11,771	82
% of total	1.2	3.2
# remaining wounds	542,921	1,585
% healed at level	91.7	87.8
Exclude # wounds patients that underwent amputation	4,455	47
% of total	0.4	1.8
# remaining wounds	538,466	1,538
% healed at level	92.5	90.2
Exclude # wounds patients converted palliative	1,149	109
% of total	0.1	4.2
Final # remaining wounds	538,352	1,429
% healed at level	92.5	97.1

Table 4. ITT heal rates at patient and wound level

2014–2015	2006–2009	
117,517/295,046	471/763	Patient level
60.2%	61.7%	
498,113/667,291	1,388/1,788	Wound level
74.6%	77.6%	

There are, however, a variety of other designs which account for nonadherence and measure the effect of the treatment as delivered, often referred to as "as-received analysis."[18] In this study, patients are not randomly assigned and it is assumed that all patients will be enrolled in the protocol. There are many structure and process issues that are also involved in the ultimate outcome which can lead to withdrawal from treatment, nonadherence, and missing data. The authors chose to borrow and apply this rigid methodology to wound healing outcomes reporting to have consistent, comparable and reproducible results. Since this study did remove wounds with days from the first to the last assessment was less than 7 days, and those patients without documented wounds, the technical term for our analysis would be a modified ITT method.[19] The healing rate for a pure ITT without any exclusions is included for comparison although it has less clinical significance. There has been much conversation about the use of a modified ITT methodology in the literature and the majority of the debate surrounds pharmaceutical trials. The exclusion of wounds with less than seven days of treatment was included because these wounds were only seen in the clinic one time and did not "receive the drug," in this case, a wound treatment protocol. Patients without any documented wound on chart review and those in treatment at the time of the closure of the analysis are self-evident. In a most recent review of this subject, there is still controversy as to the best definition of modified ITT and the authors are mostly concerned about the impact of including ITT and mITT papers in a single systematic review.[20] To address this concern, we have included for completeness, all exclusions from the total population of patients presenting in order for the readers to evaluate and hopefully dialogue about the best reporting methods for our industry moving forward.

There are many positive benefits from using ITT methodology. It reduces bias as mentioned before and allows for the potential to compare published studies from various sources. It preserves sample size and limits inferences based on arbitrary subgroup reporting. On the negative side, ITT provides a conservative estimate for the effect of treatment. In addition, heterogeneity can be introduced when dropouts, and noncompliant subjects are included in the analysis. There are statistical methods, including propensity scoring, which attempt to adjust for observed confounding variables.[21] Likewise some have used instrumental variable analyses to attempt to correct for unmeasured confounders or hidden bias.[22,23]

Table 5. Healing rates across provider type during 2006–2009 data sets.

Provider	Wounds healed/total wound	Percentage healed
Senior physician	425/551	77.1%
Junior faculty	262/346	75.7%
APN	694/891	77.9%

ITT methodology.

Of the many metrics that can be measured in wound care, healing rates, have been the most widely utilized and published. Issues arise, however, when the actual methodology employed in the study is not clearly defined. For example, in many data sets, if a patient is not evaluated within a 30-day window, they are dropped from the data set and recorded as lost to follow-up. That same patient might return on day 60 and be recorded as a new patient/wound. Some authors have chosen to exclude patients that died, moved, switched providers or were enrolled in palliative care programs. While there are reasons to analyze the data without those patients, these exclusions reduce the denominator and elevate the reported healing rate.

Previously published wound healing outcomes have ranged from 38%[9] to 88%, with one practice reporting a healing rate of 100%[23–26] suggesting issues associated with healing rate uniformity. The differences are more likely secondary to reporting variation than widespread clinical practice variation. There have been efforts to use large, multicenter databases to analyze healing outcomes retrospectively in the literature. Kantor and Margolis, established the accuracy of using such a database through a chart extraction validation process.[24] More recently efforts have been made to use large data sets to analyze both costs and wound healing rates.[25] These authors quote a similar healing rate of 65.8% as reported in this study but excluded patients lost to follow-up. Attempts are now being made to not only analyze the outcomes, but to begin to use big data to predict outcomes early in the treatment cycle for specific wound etiologies.[26,27]

A research question was developed for this study that posits whether the use of a repeatable, evidenced-based treatment plan for patients with nonhealing wounds is effective and reproducible. Internal validation was conducted using previously published data from the same clinical team and site of care and is described in a previously published manuscript.[9] We tested if external validation was possible using a similar clinical guideline at multiple sites of care and across a broad range of providers. The results imply that this is possible.

The concept of comprehensive healthcare quality outcomes was proposed by Donabedian and these concepts were incorporated into this analysis.[8] His classic work analyzed quality healthcare by measuring structure, process and outcomes. Measures of structure include facilities, equipment, human resources, pay scale, management, and other variables that impact the final result but are not directly tied to care. Process measures include the diagnosis, treatment, and education provided by not only the clinician, but the patient and their care providers as well. The outcomes can be measured at the patient or population level and include changes in health status, knowledge, behavior and satisfaction with the care provided.[28] To demonstrate the combination of the classic Donabedian

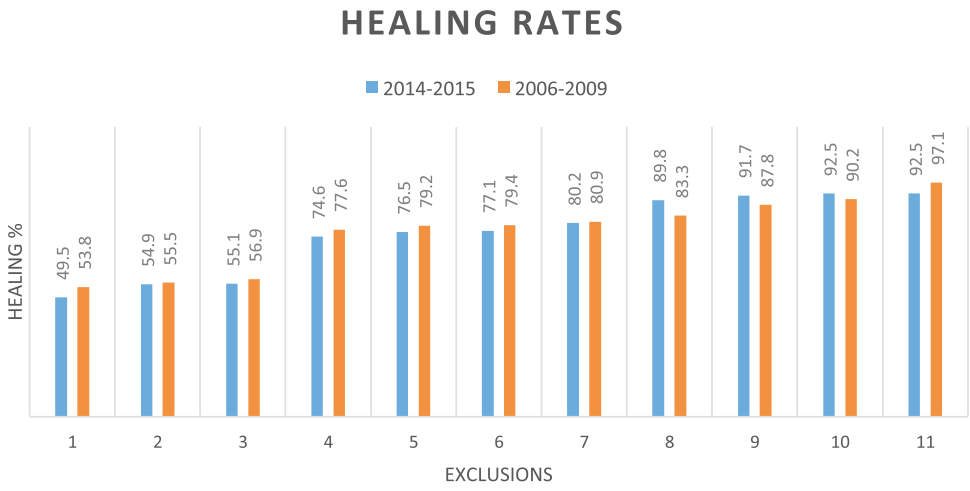

Figure 1. Healing rates. 1, total population; 2, cases active at study closure; 3, now wound present; 4, one visit (modified intent-to-treat); 5, patient died; 6, patient moved; 7, transferred provide; 8, transferred facility; 9, lost to follow-up; 10, amputated; 11, palliative care. [Color figure can be viewed at wileyonlinelibrary.com]

outcomes research approach within the ITT framework, the results from Table 3 will be described at each level of granularity taking into account the potential for bias, and the quality implications at a structure, process and outcomes level. Evaluating the healing rate at the total population level might reflect the demographics of the center, teaching versus private hospital status, bed size, and potentially a high risk patient group with special clinical needs. Authors have pointed to the importance, but rare inclusion of, antecedents of medical care, such as patient personal characteristics and their environmental context when trying to link outcomes with process and structure of care.[29] Almost a full 25% of wounds were excluded due to the patient having only one visit or being recorded as a consult only. There is currently no baseline data in the literature to benchmark this result. One reasons for consult only could be inadequate education and communication to the referral base as to the type of cases the center can manage. Another plausible explanation, however, could be that the provider or center felt that the case was too complex for their level of expertise and they were referred on. In the future, this ratio should undergo further detailed analysis to include patient demographic, insurance status, age, wound type and other potential metrics to ensure equity to access and transparency in case selection.

Results should be further analyzed as there are many outcomes outside those directly influenced by the provider such as death or patients being lost to follow-up. These exclusions speak to the structure and process of care as much as they do clinician skill and patient adherence. Adjusting for each of these parameters and the associated healing rate, can provide a window into the overall comprehensive quality of the program, both clinical and administrative, which can identify areas of opportunity to enhance the quality of overall care. The next level of exclusion was for patients that died. While some patients had wounds that healed when they died the ratio of the total number of wounds from patients that died from the total might reflect treating patients that should have been moved to palliative care earlier or whom treatment in an advanced wound care center was inappropriate. To maintain transparency in the future, these cases need to be identified and reported so that trends and comparisons to risk adjustment scores, and so forth. can be performed. Patients with wounds that transfer to other providers and/or health systems might allow for a more detailed look into process and structure. If patients perceive that their care is stagnating or do not feel clear communication between patient and provider is occurring, they might be more apt to transfer to another center. Clearly there are many network and other insurance issues that could be at play in this cohort as well but further details need to be collected in the future to tease out this trend. In this study, a higher percentage of cases transferred care in the large wound care network. This might reflect the tertiary referral practice in the 2006–2009 data sets and the inability for those patients to find any higher level of care. The lost to follow-up category provides a potential wealth of information to be learned at the provider and center level. Is there inadequate call backs for patients that fail to show up? Are patients recorded as lost to follow-up but have left for other reasons? Perhaps the wound healed and they did not feel a reason to return, or it may be that other factors such as the cost of transportation to and from the center was not sustainable. As we move away from a purely treatment focused payment system, it will be imperative that we understand, record, and manage this level of detailed data from our centers.

The healing rates in this study, which is the largest published cohort of wounds in the literature to date, demonstrated comparable healing rates between a single center academic dedicated team and a large national footprint of clinics managed by a wound care management services company. While not explicitly tested here, we suspect that the parity in healing rate between the highly specialized academic team and the national sample comprised largely of part-time panel physicians is driven by the use of standard guidelines and wound clinic management. The primary author was also involved in the past in creating the guidelines used at the corporate clinics which provides another reason that outcomes should have been consistent but provides further support to the scalability and reproducibility of the process. A visual comparison of the healing rates across the cohorts is shown in Figure 1 for a

more direct visual assessment. The literature supports that healing rates and the quality of overall care is improved with high volume practices that specialize in delivering wound care.[30–32] Future work will look into more granularity at each cohort level, improved predictive analytics and further validation of both the clinical pathway being used, and the infrastructural support system used to operationalize the care. In addition, overall population based healing rates and recidivism will need to be assessed to further validate the importance both clinically and economically of wound care clinics. We are currently working on risk stratification tools and hope to be able to create a wound scoring system that would allow both the patient and provider to gain insight into the percentage chance for healing, predicted time frame for closure, and potential impact on morbidity and quality of life as a result of choosing a specific therapeutic pathway. Going back to the Oncology analogy, a TNM scoring system for wound care would be helpful. Lastly, identifying outliers, those who have a very unlikely chance for healing, would allow patient and provider to weigh the risk/benefit profile of therapy and potentially aide in the decision for a more palliative approach.

SUMMARY

Wound care has become a growing specialty with an increasing patient volume and a plethora of available, but often costly, treatment options. The ultimate outcome metric for these patients is complete wound healing. There are other surrogate endpoints that are currently under consideration but at this time, not fully endorsed by regulatory agencies. Healing rates can be misleading without a clear understanding as to the inclusion/exclusion criteria that make up the numerator and denominator used. In this study, a modified ITT metric was employed across two very different care settings. An academic medical group practicing full time wound care, in a satellite community hospital was compared to a large wound care management company providing wound care across 626 hospitals in the US. The distribution of outcomes across the data sets was extremely comparable indicating that when utilizing agreed on protocols in a well-managed program with processes and infrastructure, consistent high quality outcomes are achieved. Using a modified ITT framework to assess wound healing will allow not only clinicians and providers, but also other key stakeholders in the healthcare environment to compare outcomes. While these findings advance the field of wound outcomes research, subsequent analyses are underway that will extend the field's ability to effectively risk stratify and understand cost patterns in the wounded population. Such analyses include aggregation of clinical and cost data as well as the use of predictive modeling to identify high risk patients with the express purpose of continuing to promote the practice of high quality value driven wound care.

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